The prevalence and impact of thrombocytopenia, anaemia and leucopenia on sustained virological response in patients receiving hepatitis C therapy: evidence from a large 'real world' cohort

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Author Names:

Huan Wang[1], Hamish Innes[2,3], Sharon J. Hutchinson[2,3], David J Goldberg[2,3], Samuel Allen[5], Stephen T Barclay[6], Peter Bramley[7], Raymond Fox[8], Andrew Fraser[9], Peter C. Hayes[10], Nicholas Kennedy[11], Peter Mills[8], John F. Dillon[4]

Author Affiliations:

[1]Dundee Epidemiology and Biostatistics Unit, University of Dundee, U.K.

[2]School of Health & Life Sciences, Glasgow Caledonian University, U.K.

[3]Health Protection Scotland, Glasgow, U.K.

[4]Division of Cardiovascular & Diabetes Medicine, Medical Research Institute, Ninewells Hospital and Medical School, Dundee, U.K.

[5]Crosshouse Hospital, Kilmarnock, UK

[6]Walton Liver Clinic, Glasgow Royal Infirmary, Glasgow, UK

[7]Department of Hepatology, Stirling Community Hospital, Stirling, UK

[8]Gartnavel General Hospital, Glasgow, UK

[9]Aberdeen Royal Infirmary, Aberdeen, UK

[10]Royal Infirmary Edinburgh, Edinburgh, UK

[11]Monklands Hospital, Lanarkshire, UK

Corresponding Author:

Dr Huan Wang

Dundee Epidemiology and Biostatistics Unit

Population Health Sciences, School of Medicine

University of Dundee, Dundee

DD1 9SY, U.K.

Tel: + (44) 1382 383198

Email: h.wang@dundee.ac.uk

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Abstracts

Objectives

To explore the extent of thrombocytopenia (TCP), anaemia, and leukopenia in patients with hepatitis C and evaluate how they impact the management of antiviral therapy (AVT), the attainment of sustained virological response (SVR), and some therapy-related adverse events.

Materials and Methods

The Scottish Hepatitis C Clinical Database was used in this retrospective study. The prevalence of TCP, anaemia, and leukopenia were evaluated. The impact of the three deficiencies on AVT management, serious adverse events, and SVR attainment were assessed in patients received therapy.

Results

The prevalence of TCP, anaemia, and leukopenia were 18.5%, 0.9%, and 0.2% among 4,907 treated patients at baseline, increasing to 72%, 25.8%, and 5.4% during treatment, respectively. Dose reduction occurred in 29.3% of the patients without TCP, this percentage was higher in those with baseline TCP (53%) and in those acquired during treatment (35%). Similar results were found for anaemia and leukopenia. Baseline TCP (OR=0.67, $p<0.001$) and baseline anaemia (OR=0.43, $p=0.03$) were identified as risk factors associated with lower SVR rate, acquired TCP and anaemia were not associated with reduced SVR.

Conclusions

Baseline TCP or anaemia increased risk of dose cessation. Patients acquired TCP, anaemia, or leukopenia during treatment did not exhibit compromised SVR rates, whereas, patients with TCP or anaemia at baseline did. The potential benefit of growth factors in maintaining

SVR rate is likely to be confined those with baseline TCP or anaemia rather than those who acquire it during therapy, where dose reduction does not appear to reduce the chance of SVR.

Keywords: chronic hepatitis, hepatitis C virus, thrombocytopenia, anaemia, leukopenia, Sustained Virological Response, dose reduction, early treatment discontinuation.

Introduction

Thrombocytopenia (TCP), anaemia, and leukopenia can be complications of chronic liver disease and considered indicators of advanced disease. The causes of them are multi-factorial including portal hypertension, hypersplenism, decreased thrombopoietin production, and virus induced bone marrow suppression [1-3]. Furthermore, TCP, anaemia, and leukopenia can also be significant side effects during hepatitis C therapy which involves peginterferon alpha and ribavirin, which was the standard of care for hepatitis C until very recently [4, 5] and with the current high cost of new direct acting antivirals may remain the mainstay of therapy for many patients for the foreseeable future. For patients with hepatitis C virus (HCV) genotype 1, the addition of protease inhibitors, boceprevir and telaprevir, has been proved to improve efficacy of antiviral therapy (AVT), but further increases the frequency as well as the severity of anaemia [6, 7]. As a result, in some patients with HCV infection, TCP, anaemia, and leukopenia prevent initiation of AVT, while in others even if they are able to initiate therapy they have to undergo dose reductions and or early treatment discontinuation (i.e. dose cessation) to manage these three deficiencies. Such sub-optimal therapy has been demonstrated to be associated with a reduced ability to achieve Sustained Virological Response (SVR) [1, 5, 6, 8-10]. The development and approval for use of second generation direct acting antivirals means that some patients have the option of interferon free regimens which avoid the cytopenias associated with interferon alpha, but the cost of these regimens means that many patients, in many countries, will continue to be treated with interferon based regimens.

Limited data exists about the extent of TCP, anaemia, and leukopenia amongst patients with HCV, both before treatment and in response to therapy. Especially for TCP, where if there is data it usually refers to normal range definitions of TCP i.e. platelet count < 150×10^9/L, which while a limit of normality, is meaningless in terms of clinical risk of

bleeding or indication for therapy reduction or cessation. However in clinical practice, TCP generally impacts management of patients with HCV at lower platelet levels and there is lack of data regarding the prevalence of TCP at these clinically meaningful values. In addition, current management of TCP, anaemia, and leukopenia in patients who are being treated for HCV is dose reduction of the AVT or even treatment cessation. There is the option to use growth factors to support platelets, leukocytes and erythrocytes but their current role is not well defined. However, there is limited small scale data to show how many patients are impacted by this and how such sub-optimal AVT impacts treatment success i.e. attainment of SVR.

The objectives of this study were to understand the extent of TCP, anaemia, and leukopenia (prevalence) among the patients with HCV in a whole country treatment population (Scotland), to evaluate how TCP, anaemia, and leukopenia impact the management of AVT, as well as to assess the SVR rates and some other therapy related adverse events (on-treatment bleeding, hepatic decompensation, sepsis and thromboembolic events) among the patients received AVT for HCV, doing this for the first time at a national level avoiding the selection biases associated with specialist centres treating more advanced disease.

Materials and methods

This retrospective descriptive database study is based on the National HCV Clinical database held at Health Protection Scotland (HPS) who collected data since year 2002 from patients diagnosed with active hepatitis C in 11 Scottish National Health Service (NHS) board areas running HCV treatment clinics [11]. Patients were defined as a unique combination of forename initial, surname soundex, date of birth, and gender. All patients in the database who

had a record of a positive PCR test for HCV were initially included. Among the included patients, the haematology test records with missing platelet count, haemoglobin level or white cell count were excluded.

The patients who received AVT were selected to further explore how TCP, anaemia, and leukopenia impacted the management of AVT (i.e. treatment dosing), SVR attainment, and the onset of serious adverse events. As part of routine clinical practice, blood counts are monitored before treatment, during, end of treatment (that would identify dose reductions and dose cessations), and at 6 months post treatment (that would identify SVR). For the patients who were treated twice or more, only the latest treatment was considered. The platelet count, haemoglobin level and white cell count prior to the initiation of AVT were considered as baseline values. The lowest platelet count, haemoglobin level, and white cell count during treatment were considered as nadir values during AVT.

Continuous variables were summarised as median with interquartile range and categorical variables as frequencies with percentages. The prevalence at baseline of TCP, anaemia, and leukopenia were determined both in the patients without AVT and in those who received AVT. Baseline refers to the first attendance - with TCP, anaemia and leukopenia defined as according to mean laboratory test results within a 3 month window around this first attendance date. Given that in clinical practice TCP generally impacts management at lower platelet levels than the textbook clinical definition i.e. platelet count $< 150 \times 10^9$/L, the prevalence of TCP was evaluated in the following ranges of platelet count: (1) 100 - 150 $\times 10^9$/L; (2) 75 - 100 $\times 10^9$/L; (3) 50 - 75 $\times 10^9$/L; (4) 25 - 50 $\times 10^9$/L; (5) $\leq 25 \times 10^9$/L. Anaemia and leukopenia were defined as a single occurrence of haemoglobin level < 10g/dl and white cell count $< 1.5 \times 10^9$/L, respectively.

Among the patients who received treatment, dose reductions and dose cessations were identified according to different severity of TCP, anaemia, and leukopenia. The impact of TCP, anaemia, and leukopenia on serious adverse events during AVT were assessed. SVR rates were also evaluated according to different status of TCP, anaemia, and leukopenia (i.e. never acquired, acquired at baseline, and acquired during AVT), and according to different management of AVT (i.e. optimal dosing, dose reduction alone, dose cessation alone, and both dose reduction and dose cessation).

Logistic regression was used to investigate the impact of baseline characteristics on SVR attainment after the last registered treatment. The age at initiation of AVT was considered as a continuous variable, and the baseline albumin level, neutrophil count, alanine aminotransferase (ALT) level, bilirubin level, haemoglobin level, and white cell count were all grouped as normal or abnormal according to their respective threshold values. Platelet count at baseline was also grouped as normal and abnormal, using the cut-off value of the clinical definition, i.e. 150×10^9/L. Variables with a p value ≤ 0.2 in the univariate logistic regression were included in the multivariate analysis [12]. A multiple imputation procedure was conducted to impute missing baseline data for the multivariate logistic regression. Every model during the model building procedure was fitted to 10 imputed datasets arising from the multiple imputation procedure. The model selection procedure was then carried out using a backward stepwise regression based on the Akaike information criterion (AIC) statistic. The model with the smallest AIC was considered the optimal model. The Hosmer-Lemeshow goodness of fit test [12] for logistic regression was carried out to see how well the final model fitted the data. Data handling and statistical analyses were conducted in R (version 3.2.0, http://cran.r-project.org/).

Results

Patients

Overall, there were 18,603 HCV antibody positive patients in the database. The 4,743 patients who had no record of a positive HCV PCR test were excluded. This group are a combination of those who did not attend follow up or had spontaneous resolution of their HCV infection. Another 3,034 patients were also excluded because of missing records of platelet count, haemoglobin level, or white cell count. In the final cohort, there were 10,826 patients with chronic HCV infection, of whom 7,700 (71%) were male, 10,135 (94%) were white ethnicity, 4,343 (40%) were with HCV genotype 1, 4,642 (43%) were with HCV genotype 3, 193 (2%) had HIV co-infection, and 630 (6%) had previous AVT experience. In terms of disease stage, 1,629 (15%) had established cirrhosis at baseline. The patients received AVT were older than those without AVT. **The duration of AVT was 24 or 48 weeks for the patients who were treatment naïve, and it was not extended for those who had previous AVT experience. The patients with HCV genotype 1 were not likely to proceed to antiviral therapy, while those with HCV genotype 3 were more likely to response to interferon. Among the 193 patients with combined infection of HCV and HIV, 86 received HCV antiviral therapy, where most of them (75 of 86) were treated by peginterferon and ribavirin, 7 received combined treatment of peginterferon, ribavirin and telaprevir, 3 received peginterferon alone, and only 1 received combined treatment of interferon and ribavirin.** The other characteristics among these two groups were similar (details shown in Table 1).

Prevalence

The prevalence of TCP (in different ranges), anaemia, and leukopenia are shown in Table 2. There were more patients whose platelet count were below 75×10^9/L in the "No-AVT" group than that at baseline in the AVT group, which could be one reason that prevented initiation of AVT for some patients. The prevalence of anaemia in the "No-AVT" group (5%, 95% CI: 4.4% - 5.5%) was also much higher than that at baseline in the AVT group (0.9%, 95% CI: 0.7% - 1.2%). Among the 4,907 treated patients, the prevalence of TCP, anaemia, and leukopenia at any point during AVT were much higher at 72% (95% CI: 70.7% - 73.3%), 25.8% (95% CI: 24.6% - 27%), and 5.4% (95% CI: 4.7% - 6%), respectively.

Impact of TCP, anaemia, and leukopenia on AVT dosing

The numbers and percentages of patients who received optimal dosing, who underwent dose reduction or dose cessation, according to different status of TCP, anaemia, and leukopenia are shown in Table 3. Overall, among the 4,907 treated patients, 2,338 patients (47.6%) received optimal dosing, 1,802 patients (36.7%) underwent dose reduction, and 1,367 patients (27.9%) underwent dose cessation. **There was evidence that 600 patients underwent both dose reduction and cessation. The detailed percentages are shown in the last column of Table 3.** The patients with TCP (at baseline or acquired during AVT) had higher risk of undergoing dose reduction than those never had TCP (53% at baseline, 35% during AVT, 29.3% for non-TCP). Similar results can be found for anaemia and leukopenia. However, only baseline TCP and baseline anaemia increased the risk of undergoing dose cessation.

Table 4 shows the detailed number of patients who underwent dose reduction and or dose cessation. Among all the 1,802 dose reductions, 162 (9%) were associated with TCP, 289 (16%) were associated with anaemia, and only 13 (0.7%) were associated with leukopenia. Among the 1,367 dose cessations, 42 (3.1%) were associated with TCP, 29 (2.1%)

were associated with anaemia, and only 8 (0.6%) were associated with leukopenia. Some reductions or cessations were associated with more than one of the three deficiencies, since the patients could have all three. The patients who had an abnormal platelet count at baseline were more likely to undergo TCP-related dose reduction and or TCP-related dose cessation than those who had a normal baseline platelet count (reduction: 24.6% vs 3.3%; cessation: 10.8% vs 0.5%). The proportion of patients undergoing anaemia-related dose reduction among the patients who had abnormal haemoglobin level at baseline was around two times higher than that among those with normal haemoglobin level at baseline (30.8% vs 15.8%). All leukopenia-related reductions and cessations occurred among the patients with a normal white cell count at baseline (reduction: 0.7%; cessation: 0.6%). However, the number of patients with an abnormal haemoglobin level (only 46 patients) or an abnormal white cell count (only 11 patients) at baseline was quite small.

Impact of TCP, anaemia, and leukopenia on serious adverse events on therapy

The number of patients who had some serious adverse events recorded in the database (on-treatment bleeding, sepsis, hepatic decompensation, and thromboembolic events) on therapy are shown in Table 5. Overall the rates were low and not strongly associated with TCP, anaemia, or leukopenia, but this may have been confounded by dose alteration. Among the 4,907 treated patients, 110 patients (2.2%) had on-treatment bleeding, 3 (< 0.1%) had sepsis, 5 (< 0.1%) had hepatic decompensation, and 2 (< 0.1%) had thromboembolic events. The patients with both TCP and leukopenia had the highest risk of on-treatment bleeding (5.43%). The other three adverse events all occurred in patients with either TCP alone or with both TCP and anaemia.

Impact of TCP, anaemia, and leukopenia on SVR attainment

The SVR rates of the patients attained, according to different status of TCP, anaemia, and leukopenia, are shown in Table 6. The patients who never had TCP and the patient who acquired TCP during AVT had similar overall SVR rates (55.8% and 55.5%), while those who had baseline TCP had a much lower SVR rate of 36.5% (95% CI: 33.4% - 39.7%). In the "Non-TCP" group and the "Acquired TCP during AVT" group, the patients whose dose level were reduced had similar SVR rate as those who received optimal dosing (70.3% vs 68.7%; 66.7% vs 61.4%). Similar results were found for anaemia and leukopenia. However, there were no patients who had baseline leukopenia and underwent dose cessation alone, therefore the SVR rate in this group was not reported. Moreover, there were only 2 patients who had baseline leukopenia and received both dose reduction and dose cessation, and 1 of them achieved SVR, which lead to a higher SVR rate of 50% (95% CI: 1.3% - 98.7%) in this group than those who never had leukopenia and those who acquired leukopenia during AVT. Clearly the small number makes it impossible to draw any conclusion.

Overall Risk factors for SVR attainment

In the univariate analysis (Table 7), baseline TCP (OR = 0.46, 95% CI: 0.4 - 0.53, $p < 0.001$) and baseline anaemia (OR = 0.25, 95% CI: 0.13 - 0.51, $p < 0.001$) were inversely associated with SVR, whereas baseline leukopenia did not significantly reduce the SVR rate (OR = 0.34, 95% CI: 0.09 - 1.3, $p < 0.115$). In the multivariate analysis, baseline TCP (OR: 0.67, 95% CI: 0.56 - 0.81, $p < 0.001$) and baseline anaemia (OR: 0.43, 95% CI: 0.2 - 0.92, $p = 0.03$) were identified as risk factors associated with lower SVR rate. The variables with p values greater than 0.05 (gender and baseline neutrophil) were kept in the final model since they could provide some useful information as well as make the model achieve the smallest value of

AIC. A 10-fold Hosmer-Lemeshow goodness of fit test for the final multivariate logistic regression model gave a *p* value 0.148, which indicated the model fitted the data well.

Discussion

This study determined the prevalence of TCP, anaemia, and leukopenia, both prior to and during treatment of HCV, among all the known patients with HCV in a whole country, Scotland. The rate of mild baseline TCP was much higher than the reported rate of cirrhosis, while there may have been under ascertainment of cirrhosis due to the removal of a requirement for liver biopsy to qualify for treatment in the later stages of the cohort and limited availability of non-invasive assessment of liver fibrosis, it is unlikely that the rate was as high as the rate of TCP. It is more likely that alcohol and other life style factors may have been having an effect. The much higher prevalence of TCP, anaemia, and leukopenia during AVT confirmed unsurprisingly that the three deficiencies were all side effects triggered by interferon based therapy hepatitis C.

Among the patients who received treatment for HCV, the impact of TCP, anaemia, and leukopenia on the management of AVT and on the SVR attainment were also evaluated. TCP, anaemia, and leukopenia all increased the risk of undergoing dose reduction. Only baseline TCP and baseline anaemia increased the risk of undergoing dose cessation. Acquirement of TCP, anaemia, and leukopenia during AVT did not have significant influence on SVR attainment, while the presence of TCP and or anaemia at baseline significantly reduced the chance to achieve SVR. This can be explained by the higher risk of undergoing dose cessation in the patients with baseline TCP or baseline anaemia, which can directly reduce the likelihood of SVR but also important is that these parameters are surrogate markers of cirrhosis, which is a well-known factor for reduced chance of SVR. The reasons

of undergoing dose reduction were complicated. The majority of the reductions were triggered by patient-related clinical side effects during treatment, while some reductions were due to blood-test-triggered reductions such as TCP, anaemia, or leukopenia, which can be regarded as drug toxicity. The patients who demonstrated some toxicity might have been exposure up to and beyond their optimum dose and dose reduction brought them to optimum dose, but those without toxicity might not have been exposure to their optimum dose, this may in particular be true of ribavirin and to a less extent interferon. This may be the reason that patients who underwent dose reduction had similar or even slightly higher SVR rate than those who received apparently optimal dosing without dose reduction. **In this cohort, there was no documented cases of growth factors being used. The structure of the database means these may not have been well recorded. However, very few patients, if any, received any growth factor support such as erythropoietin, granulocyte colony stimulating factor or eltrombopag.** So the vast majority of patient events in this cohort related to TCP, anaemia, or leukopenia were managed by dose reduction. It is very clear from our data that those patients who had no TCP, anaemia, or leukopenia at baseline but acquired it during therapy were managed with dose reduction and had no reduction in their rate of SVR. This suggests that growth factor support is unnecessary for most patients with acquired TCP, anaemia, or leukopenia, and the role of these agents lies in improving baseline abnormalities in the hope that this might improve SVR attainment. **The assessment of the role of growth factors according to timing of its use is out of the scope of this study.** The co-existence of anaemia seems to increase the risk of sepsis, hepatic decompensation and thromboembolic events among TCP patients.

In summary we have shown in a very large cohort of unselected patients representative of a whole nation the rates of thrombocytopenia, anaemia, and leukopenia in HCV infection patients and demonstrated what happens to these during interferon based

therapy. Patients having pre-treatment thrombocytopenia, anaemia, or leukopenia had increased the risk of undergoing dose cessation and a reduced chance of SVR. However, acquiring thrombocytopenia, anaemia, and leukopenia during treatment did not have significant impact on attaining SVR, when managed with dose reduction compared to those who did not need dose reduction. This was achieved in a cohort with very little use of growth factor support before or during treatment. The potential benefit of growth factors in maintaining SVR rate is likely to be confined to those with baseline thrombocytopenia or anaemia rather than those who acquired it during therapy, unless they do not respond to dose reduction. Overall, patients who acquire thrombocytopenia, anaemia, and leukopenia during therapy can be managed first line with dose reduction. If this is successfully and avoids dose cessation then there is no reduction in the SVR rate.

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JD, HW designed the study and wrote the manuscript. HW collected and analysed the data. HI, SH, DG, SA, SB, PB, RF, AF, PH, NK, PM, and JD revised it critically.

Conflicts of interests

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Tables

Table 1. Patient demographics summary.

Characteristics	Total (n = 10,826)	No AVT (n = 5,919)	AVT (n = 4,907)
Age[1] (range)	45 (38 – 52)	44 (37 – 50)	47 (39 – 54)
Gender			
Male	7,700 (71%)	4,188 (71%)	3,512 (72%)
Female	3,125 (29%)	1,730 (29%)	1,395 (28%)
Unknown	1 (< 0.01%)	1 (< 0.01%)	--
Ethnicity			
White	10,135 (94%)	5,673 (96%)	4,462 (91%)
Non-white	577 (5%)	180 (3%)	397 (8%)
Unknown	114 (1%)	66 (1%)	48 (1%)
HCV genotype			
1	4,343 (40%)	2,392 (40%)	1,951 (40%)
3	4,642 (43%)	2,134 (36%)	2,508 (51%)
Others	615 (6%)	284 (5%)	331 (7%)
Unknown	1,226 (11%)	1,109 (19%)	117 (2%)
HIV status			
Positive	193 (2%)	107 (2%)	86 (2%)
Negative	6,761 (62%)	3,392 (57%)	3,369 (69%)
Unknown	3,872 (36%)	2,420 (41%)	1,452 (29%)
Cirrhosis at entry	1,629 (15%)	1,013 (17%)	616 (13%)
Previous AVT experienced	630 (6%)	--	630 (16%)

[1]Age at 2014/01/01.

Table 2. Prevalence of TCP, anaemia, and leukopenia for patients without AVT and patients received AVT (at baseline and during AVT).

Characteristic	Range	Prevalence[1] (95% CI)		
		No AVT	AVT (n = 4,907)	
		(n = 5,919)	Baseline	During AVT
Platelet count	100 – 150 ($\times 10^9$/L)	12.7 (11.8 – 13.5)	12.3 (11.4 – 13.2)	33.5 (32.2 – 34.9)
	75 – 100 ($\times 10^9$/L)	3.8 (3.3 – 4.2)	3.1 (2.6 – 3.6)	16.4 (15.3 – 17.4)
	50 – 75 ($\times 10^9$/L)	3.4 (2.9 – 3.8)	2 (1.6 – 2.4)	10.7 (9.9 – 11.6)
	25 – 50 ($\times 10^9$/L)	2.6 (2.2 – 3.0)	0.7 (0.5 – 0.9)	8 (7.2 – 8.7)
	$\leq$ 25 ($\times 10^9$/L)	0.9 (0.6 – 1.1)	0.3 (0.1 – 0.4)	3.4 (2.9 – 3.9)
	Total (<150$\times 10^9$/L)	23.2 (22.2 – 24.3)	18.5 (17.4 – 19.5)	72 (70.7 – 73.3)
Haemoglobin level	< 10 g/dl	5 (4.4 – 5.5)	0.9 (0.7 – 1.2)	25.8 (24.6 – 27)
White cell count	< 1.5 × 10^9/L	0.3 (0.2 – 0.5)	0.2 (0.1 – 0.4)	5.4 (4.7 – 6)

[1]Prevalence is expressed as percentage.

Table 3. Number of patients received optimal dosing, underwent dose reduction or dose cessation, according to different status of TCP, anaemia, and leukopenia.

	Total number	Optimal dosing (%)	Dose reductions (%)	Dose cessations (%)	Dose reduction & cessation (%)
TCP					
Non-TCP	1,352	689 (51%)	396 (29.3%)	400 (29.6%)	**133 (9.8%)**
present at baseline	906	277 (30.6%)	480 (53%)	342 (37.7%)	**193 (21.3%)**
Acquired during AVT	2,649	1,372 (51.8%)	926 (35%)	625 (23.6%)	**274 (10.3%)**
Anaemia					
Non-anaemia	3,627	1,892 (52.2%)	1,096 (30.2%)	1,027 (28.3%)	**388 (10.7%)**
present at baseline	46	14 (30.4%)	26 (56.5%)	14 (30.4%)	**8 (17.4%)**
Acquired during AVT	1,234	432 (35%)	680 (55.1%)	326 (26.4%)	**204 (16.5%)**
Leukopenia					
Non-leukopenia	4,640	2,244 (48.4%)	1,649 (35.5%)	1,296 (27.9%)	**549 (11.8%)**
present at baseline	11	3 (27.3%)	8 (72.7%)	2 (18.2%)	**2 (18.2%)**
Acquired during AVT	256	91 (35.5%)	145 (56.6%)	69 (27%)	**49 (19.1%)**
Total	4,907	2,338 (47.6%)	1,802 (36.7%)	1,367 (27.9%)	**600 (12.2%)**

Table 4. Dose reductions and dose cessations associated with TCP, anaemia, and leukopenia, according to different platelet count, haemoglobin level, and white cell count.

TCP						
Baseline platelet ($\times 10^9$/L)	**Nadir platelet during AVT ($\times 10^9$/L)**	**Total no. patients**	**Dose reductions**		**Dose cessations**	
			Total	**TCP-related**	**Total**	**TCP-related**
Normal (≥ 150)	≥ 150	1,352	396	1 (0.3%)	400	0 (0%)
	100 – 150	1,502	486	4 (0.8%)	358	0 (0%)
	75 – 100	635	221	4 (1.8%)	136	0 (0%)
	50 – 75	307	119	13 (10.9%)	69	1 (1.4%)
	25 – 50	125	65	17 (26.2%)	37	1 (2.7%)
	< 25	80	38	5 (13.2%)	25	3 (12.0%)
	Total	4,001	1,322	44 (3.3%)	1,025	5 (0.5%)
Abnormal (< 150)	≥ 150	22	8	0 (0%)	8	0 (0%)
	100 – 150	144	64	1 (1.6%)	48	0 (0%)
	75 – 100	169	81	6 (7.4%)	55	3 (5.5%)
	50 – 75	220	100	20 (20.0%)	74	7 (9.5%)
	25 – 50	266	176	66 (37.5%)	113	14 (12.4%)
	< 25	85	51	25 (49.0%)	44	13 (29.5%)
	Total	906	480	118 (24.6%)	342	37 (10.8%)
Total		4,907	1,802	162 (9%)	1,367	42 (3.1%)
Anaemia						
Baseline Hb[1] (g/dl)	**Nadir Hb[1] during AVT (g/dl)**	**Total no. patients**	**Dose reductions**		**Dose cessations**	
			Total	**Anaemia-related**	**Total**	**Anaemia-related**
Normal (≥ 10)	≥ 10	3,627	1,096	55 (5%)	1,027	5 (0.5%)
	8 – 10	1,023	568	193 (34%)	240	12 (5%)
	< 8	211	112	33 (29.5%)	86	12 (14%)

	Total	4,861	1,776	281 (15.8%)	1,353	29 (2.1%)
Abnormal (< 10)	≥ 10	14	8	0 (0%)	8	0 (0%)
	8 – 10	27	15	6 (40%)	6	0 (0%)
	< 8	5	3	2 (66.7%)	0	0 (0%)
	Total	46	26	8 (30.8%)	14	0 (0%)
Total		4,907	1,802	289 (16%)	1,367	29 (2.1%)

Leukopenia

Baseline Wcc[2] (g/dl)	**Nadir Wcc[2] during AVT (g/dl)**	**Total no. patients**	**Dose reductions**		**Dose cessations**	
			Total	**Leukopenia-related**	**Total**	**Leukopenia-related**
Normal (≥ 1.5)	≥ 1.5	4,640	1,649	7 (0.4%)	1,296	6 (0.5%)
	< 1.5	256	145	6 (4.1%)	69	2 (2.9%)
	Total	4,896	1,794	13 (0.7%)	1,365	8 (0.6%)
Abnormal (< 1.5)	≥ 1.5	3	1	0 (0%)	0	0 (-)
	< 1.5	8	7	0 (0%)	2	0 (0%)
	Total	11	8	0 (0%)	2	0 (0%)
Total		4,907	1,802	13 (0.7%)	1,367	8 (0.6%)

[1]Hb: haemoglobin level; [2]Wcc: white cell count.

Table 5. Profile of adverse events on treatment, according to different combinations of any occurrence of TCP, anaemia, and leukopenia.

Patient group	Total number	Bleeding	Sepsis	Hepatic decompensation	Thromboembolic events
None	1,094	19 (1.74%)	0	0	0
TCP only	2,430	53 (2.18%)	2 (0.08%)	2 (0.08%)	1 (0.04%)
Anaemia only	235	6 (2.55%)	0	0	0
Leukopenia only	11	0	0	0	0
TCP & Anaemia	881	23 (2.61%)	1 (0.11%)	3 (0.34%)	1 (0.11%)
TCP & Leukopenia	92	5 (5.43%)	0	0	0
Anaemia & Leukopenia	12	0	0	0	0
TCP & Anaemia & Leukopenia	152	4 (2.63%)	0	0	0
Total	4,907	110 (2.24%)	3 (0.06%)	5 (0.1%)	2 (0.04%)

Table 6. SVR rates according to different status of TCP, anaemia, and leukopenia, and different management of AVT.

	SVR rate in percentage (95% CI)				
	Optimal dosing	**Reduction alone**	**Cessation alone**	**Reduction & cessation**	**Overall**
TCP					
Non-TCP	68.7 (65.0-72.1)	70.3 (64.4-75.8)	20.6 (15.9-26.0)	30.8 (23.1-39.4)	55.8 (63.1-58.4)
Acquired at baseline	53.8 (47.7-59.8)	47.7 (41.8-53.7)	6.7 (3.3-12.0)	18.1 (13.0-24.3)	36.5 (33.4-39.7)
Acquired during AVT	61.4 (58.8-64.0)	66.7 (63.0-70.3)	27.9 (23.3-32.9)	34.3 (28.7-40.3)	55.5 (53.6-57.4)
Anaemia					
Non-anaemia	63.8 (61.6-66.0)	62.4 (58.7-66.0)	20.8 (17.7-24.2)	23.5 (19.3-28.0)	51.7 (50.0-53.3)
Acquired at baseline	35.7 (12.8-64.9)	16.7 (3.6-41.4)	0.0* (--)	25.0 (3.2-65.1)	21.7 (9.8-33.7)
Acquired during AVT	58.3 (53.5-63.0)	65.5 (61.1-69.8)	24.6 (17.2-33.2)	37.7 (31.1-44.8)	54.4 (51.6-57.2)
Leukopenia					
Non-leukopenia	63.0 (60.9-65.0)	63.4 (60.4-66.2)	21.7 (18.8-24.8)	26.8 (23.1-30.7)	52.1 (50.7-53.6)
Acquired at baseline	33.3 (0.8-90.6)	16.7 (0.4-64.1)	--[#]	50.0 (1.3-98.7)	27.3 (1.0-53.6)
Acquired during AVT	56.0 (45.2-66.4)	61.5 (51-71.2)	5.0 (0.1-24.9)	44.9 (30.7-59.8)	52.0 (45.8-58.1)

*There were 6 patients who had baseline anaemia and underwent dose cessation, but none of them achieved SVR. [#]No patients had baseline leukopenia and underwent dose cessation alone.

Table 7. Univariate and multivariate logistic regression for analysis of risk factors for SVR.

Baseline characteristic	Univariate OR (95% CI)	*P* value	Multivariate OR (95% CI)	*P* value
Age at initiation of AVT	0.97 (0.96 – 0.98)	< 0.001	0.98 (0.98 – 0.99)	< 0.001
Gender				
Male *vs* Female	0.85 (0.75 – 0.97)	0.012	0.88 (0.77 – 1)	0.058
Ethnicity				
White *vs* Non-white	0.51 (0.41 – 0.63)	< 0.001	0.64 (0.51 – 0.8)	< 0.001
HCV genotype				
Genotype 3 *vs* 1	2.56 (2.27 – 2.89)	< 0.001	2.45 (2.16 – 2.78)	< 0.001
Others *vs* 1	2.27 (1.79 – 2.88)	< 0.001	2.3 (1.81 – 2.93)	< 0.001
HIV co-infection				
Yes *vs* No	0.75 (0.49 – 1.16)	0.198	0.56 (0.38 – 0.81)	0.002
Baseline cirrhosis				
Yes *vs* No	0.41 (0.34 – 0.49)	< 0.001	0.68 (0.55 – 0.84)	< 0.001
Treatment experience				
Experienced *vs* Naïve	0.42 (0.35 – 0.5)	< 0.001	0.51 (0.42 – 0.62)	< 0.001
Baseline albumin				
Abnormal *vs* Normal	0.41 (0.31 – 0.56)	< 0.001	0.57 (0.42 – 0.77)	< 0.001
Baseline ALT				
Abnormal *vs* Normal	1.06 (0.95 – 1.19)	0.293		
Baseline bilirubin				
Abnormal *vs* Normal	0.45 (0.35 – 0.57)	< 0.001	0.7 (0.53 – 0.92)	0.01
Baseline neutrophil				
Abnormal *vs* Normal	0.42 (0.31 – 0.57)	< 0.001	0.76 (0.54 – 1.07)	0.114
Baseline TCP	0.46 (0.4 – 0.53)	< 0.001	0.67 (0.56 – 0.81)	< 0.001
Baseline anaemia	0.25 (0.13 – 0.51)	< 0.001	0.43 (0.2 – 0.92)	0.03

Baseline leukopenia	0.34 (0.09 – 1.3)	0.115

OR: odds ratio.